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Cadmium: Exposure Markers as Predictors of Nephrotoxic Effects

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Cadmium (Cd) is a cumulative element with a biological half-life of >10 years in humans. The total amount of Cd accumulated in the liver and in the kidney can be measured in vivo by neutron activation (or x-ray fluorescence), but this technique does not necessarily measure the fraction that is biologically active. At low exposure (i.e., general environmental exposure or moderate occupational exposure), blood Cd is mainly influenced by the last 2 to 3 months of exposure. Under such conditions, the Cd concentration in urine mainly reflects the amount of Cd stored in the body, particularly in the kidney. In Europe and the US, the Cd reference values are usually <2 nmol/mmol creatinine. Because most of the Cd in urine is probably bound to metallothionein, the changes in the urinary metallothionein concentration parallel those of Cd. The determination of Cd concentration in hair is of limited value because in humans it is difficult to distinguish between externally deposited and endogenous Cd. Fecal Cd is a good indicator of the oral daily intake. The results of several cross-sectional epidemiologic studies of the relation between the prevalence of renal dysfunction and Cd concentration in urine led us to propose a biological limit value for Cd of 5 and 2 nmol/mmol creatinine for adult male workers and the general population, respectively.

Indexing Terms: *metabolism/biological monitoring/renal markers/toxicology*

The metabolism of cadmium (Cd) has been reviewed recently (*1*). Exposure of the nonsmoking general population to Cd is mainly through food, whereas for smokers tobacco is also an important source of Cd exposure. In the occupational setting, inhalation of Cd-containing dust and fumes is the major route of uptake. The oral absorption rate is in the 2–7% range, with values of up to 20% for subjects with very low iron stores. A pulmonary absorption rate of 25–50% has been estimated for Cd oxide fumes. The absorption of other Cd compounds may vary greatly, depending on the chemical species and the particle size. Of circulating Cd, >90% is bound to erythrocytes.

Cd is a cumulative element with a biological half-life of >10 years in man. It accumulates mainly in the kidney and in the liver, with ~50% of the body burden in these two organs. In the general population the concentration of Cd in the kidney increases progressively with age at least until age 50–60, and then tends to decline. Liver concentration does not show a clear decrease in the elderly. Estimates of the mean body burden of nonoccupationally exposed adults range from 5 to 20 mg. The body burden of smokers is about twice that of nonsmokers. In tissues, Cd is bound mainly to metallothionein, whose production is stimulated by Cd exposure. Cd is excreted via the urine and to a smaller extent through the bile, the gastrointestinal tract, saliva, hair, nails, and breast milk.

In man, the three main targets after long-term Cd exposure are lung, bone, and kidney, but it is generally accepted that the kidney is the critical organ, i.e., the organ that exhibits the first adverse effects (*1*). High past industrial exposure may be associated with an increased risk of cancer (mainly in the lung), but confounding factors (e.g., concomitant exposure to arsenic) have not yet been adequately accounted for (*2*).

Biologic Markers of Exposure

It is possible to measure directly by neutron activation or x-ray fluorescence the amount of Cd that has accumulated in the liver and in the kidney. The technique, however, is not widely available. Indirect biologic indicators, such as Cd concentrations in blood, urine, feces, and hair, or metallothionein concentration in urine, have been proposed to assess either the current exposure or the amount of the metal accumulated in the body (internal dose). The significance of these markers can be briefly summarized as follows.

Cd in Blood

Blood Cd concentration is influenced by both the body burden and recent exposure, but several observations in the general population, in workers moderately exposed to Cd, and also experimental data suggest that Cd in blood mainly reflects the last few months of exposure. In newly exposed workers, the Cd concentration increases progressively for 4–6 months and then levels off at a value that is proportional to the average intensity of exposure (*3*). Reduction of exposure intensity is associated with a progressive decline of the Cd concentration in blood (half-time 2–3 months). However, in subjects who have been highly exposed in the past and have accumulated large amounts of Cd, the body burden may play a significant role in determining the concentration in blood (*4*).

For the general population, blood Cd is mainly influenced by the current exposure and less by the body burden, as shown by the very weak tendency of this parameter to increase with age (*5*). In nonoccupationally exposed adults who are nonsmokers, the Cd concentration in blood is generally <18 nmol/L ($\bar{x}$ = 5) (*1, 6*). Higher values (up to 44 nmol/L) have been found in smokers.

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Cd in Urine

At low exposure (i.e., general environmental exposure or moderate occupational exposure), when the total amount of Cd absorbed has not yet saturated all of the available Cd-binding sites in the body (particularly metallothionein), the Cd concentration in urine mainly reflects the amount stored in the body and particularly in the kidney. Thus, in the general population the urinary excretion of Cd progressively increases with age in parallel with the body burden until age 50–60. [In nonsmokers, it is correlated with the integrated oral daily intake as well as the body burden (*7*).] In workers moderately exposed to Cd, the urinary concentration increases with duration of exposure and is significantly correlated with the concentration in the kidney.

Once the Cd-binding sites in the body become saturated after excessive exposure, the Cd that is still absorbed cannot be further retained and is rapidly excreted in the urine. Under these conditions, urinary Cd is also influenced by recent exposure.

When Cd-induced renal tubular damage develops, a considerable increase in the urinary excretion of Cd occurs because of its loss from the renal depot. There is evidence, however, that tubular dysfunction unrelated to Cd exposure does not necessarily increase Cd excretion (*8*). In nonoccupationally exposed subjects, the Cd concentration in urine rarely exceeds 2 nmol/mmol creatinine (*9*).

Metallothionein in Urine

Because most of the Cd in urine is probably bound to metallothionein, the changes in the urinary metallothionein concentration parallel those of Cd. Before the occurrence of renal tubular damage, the urinary concentration of metallothionein is mainly an indicator of Cd body burden (*10*).

Cd in Hair

Cd accumulated in hair reflects the concentration of the metal in blood during the growth phase of the hair. However, this analysis is of limited value because in humans it is very difficult to distinguish between endogenous Cd and Cd externally deposited on the hair (*11*).

Cd in Feces

Fecal Cd is a good indicator of the daily amount of Cd ingested via food and the amount cleared from the lungs (*1*). In practice, however, it is more complicated to get access to feces than to blood and urine.

From the above considerations, we can conclude that the Cd concentration in urine is the most relevant and practical biologic indicator to estimate indirectly the amount of Cd stored in the kidney.

Threshold Effect Concentrations of Urinary Cd

Adult Male Workers

In the 1970s we performed several cross-sectional epidemiologic studies on Cd workers to investigate the relation between the prevalence of renal tubular dysfunction and Cd concentration in urine. We found that an increased excretion of low-molecular-mass proteins such as β_2-microglobulin mainly occurred when Cd concentrations in urine exceeded 10–15 nmol/mmol creatinine, corresponding to a renal cortex concentration of ~200 ppm (measured in vivo by neutron activation analysis) (*12–16*). We also noted that an increased glomerular permeability, reflected by an increased excretion of high-molecular-mass proteins, could also be detected in some Cd workers who did not present signs of tubular dysfunction.

In the framework of a recent collaborative European Community project, we examined a cohort of workers exposed to Cd and a matched control group for the presence of early renal changes. Several biologic markers were used to detect changes at different renal sites (glomerulus, proximal tubule, loop of Henle, distal tubule, and interstitium). A multiple regression analysis revealed a significant association between the Cd concentration in urine and the urinary output of several markers (*17*).

Four thresholds of urinary Cd were identified (Table 1): 2.4 nmol/mmol creatinine for the increased excretion of the prostaglandin 6-keto-$PGF_{1\alpha}$ and sialic acid; ~4 nmol/mmol creatinine for the increased excretion of the renal brush-border antigen, the enzymes *N*-acetyl-β-D-glucosaminidase and intestinal alkaline phosphatase, and high-molecular-mass proteins albumin and transferrin; ~6–7 nmol/mmol creatinine for serum β_2-microglobulin and the increased excretion of Tamm–Horsfall glycoprotein; and ~10 nmol/mmol creatinine for the increased excretion of tissue nonspecific alkaline phosphatase, the brush-border antigen HF5, the low-molecular-mass proteins retinol-binding protein and β_2-microglobulin, and the glycosaminoglycans.

The interpretation of these data for health risks requires taking into account the health significance of these renal changes and the possible confounding influence of the "healthy worker effect." The results of a

Table 1. Thresholds of urinary Cd associated with a significantly higher probability of abnormal values of several renal markers in adult male workers.

Markers	Cd conc in urine, nmol/mmol creatinine
6-keto-$PGF_{1\alpha}$	2.4
Sialic acid	2.4
Transferrin	3.6
Brush border antigen (BBA)	3.7
N-acetyl-β-D-glucosaminidase	4.0
Intestinal alkaline phosphatase	4.1
Albumin	4.1
β_2-Microglobulin (serum)	6.1
Tamm–Horsfall glycoprotein	7.0
Tissue nonspecific alkaline phosphatase	9.7
Brush border antigen HF5	10.0
Retinol-binding protein	10.4
β_2-microglobulin	11.5
Glycosaminoglycans	11.5

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5-year prospective study on Cd workers led us to conclude that the Cd-induced low-molecular-mass proteinuria, which may occur when Cd in urine exceeds 10 nmol/mmol creatinine, should be regarded as an adverse effect because it is irreversible (*18*) and associated with an exacerbation of the age-related decline in the glomerular filtration rate (*19*) and a reduction of protein-induced short-term hyperfiltration (so-called filtration reserve capacity) (*20*). So far, no prospective study has yet been carried out to assess the possible health significance of the other renal changes. We have shown, however, that in workers, a Cd body burden insufficient to cause an increased excretion of low-molecular-mass proteins (i.e., at Cd in urine <10 nmol/mmol creatinine) does not affect the baseline glomerular filtration rate and does not compromise the filtration reserve capacity of the kidney (*20*). This would suggest that for adult male workers the threshold of 10 nmol/mmol creatinine affords some protection. However, in some workers a slightly increased glomerular permeability to high-molecular-mass proteins may precede the occurrence of low-molecular-mass proteinuria (*12, 21*), and that in another type of renal pathology, diabetic nephropathy, the occurrence of a persistent albuminuria is considered a sensitive predictor of clinical nephropathy. Furthermore, as indicated above, an increased urinary excretion of various renal markers may also be observed in some workers with Cd concentration in urine <10 nmol/mmol creatinine.

Although the health significance of changes other than microproteinuria is still unknown, it seems logical to propose that occupational exposure should not allow the Cd concentration in urine to reach 5 nmol/mmol creatinine.

General Population

A more stringent guideline is justified for the general population. Until the renal changes induced by Cd have been clearly proven to be without long-term health consequences, it seems preferable to prevent their occurrence. Furthermore, we recently performed a large scale, cross-sectional epidemiologic study among >2000 subjects nonoccupationally exposed to Cd and living in different urban or rural areas of Belgium with different degrees of environmental pollution (22). After excluding subjects who had been occupationally exposed to heavy metals (Cd, Zn, Pb, or Hg), those <20 or >80 years of age, those who provided unreliable information on smoking habits or occupational exposure to heavy metals, and those whose 24-h urine collection were not considered reliable, 1699 subjects remained for the final statistical analysis. A multiple regression analysis revealed that several urinary markers (i.e., β_2-microglobulin, retinol-binding protein, *N*-acetyl-β-D-glucosaminidase activity, amino acids, calcium) were significantly associated with the Cd concentration in urine. A significant association was also found between Cd in urine and the prevalence of increased values of β_2-microglobulin, retinol-binding protein, *N*-acetyl-β-D-glucosaminidase, amino acids, and calcium in urine (after standardization for the other predictors or covariates). The likelihood of values being abnormal was 10% when Cd excretion exceeded 17–38 nmol/24 h (Table 2).

Table 2. Thresholds of urinary Cd associated with a significantly higher probability of abnormal values of several renal markers in the general population.

Markers	Cd conc in urine, nmol/24 h
Calcium	16.9
N-acetyl-β-D-glucosaminidase	24.0
Retinol-binding protein	25.8
β_2-microglobulin	27.6
Amino acids	38.3

We conclude that environmental exposure to Cd in certain areas of Belgium may induce slight renal tubular dysfunction and may probably also affect calcium homeostasis. The probability of occurrence of tubular dysfunction significantly exceeds the background concentration when Cd in urine reaches 2 nmol/mmol creatinine. This value should be regarded as the maximum tolerable internal dose of Cd for the general population. This concentration corresponds to a renal cortex concentration of ~50 ppm. In view of our knowledge of the toxicokinetics of Cd, we estimate that in nonsmokers, this concentration is attained after 50 years of an oral daily intake of Cd of ~1 μg/kg body weight.

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